

Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients

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Between 1990 and 1994, a series of prospective studies were conducted to optimize the treatment of multidrug-resistant falciparum malaria on the borders of Thailand. The tolerance of various treatment regimens containing either mefloquine 15 mg/kg (M15) or 25 mg/kg (M25) was evaluated in 3673 patients aged between 6 months and 88 years. Early vomiting (within 1 hour) is an important determinant of treatment outcome in these areas, despite re-administration of the dose. Overall, 7% of the patients vomited within an hour. Significant risk factors were age ≤ 6 years (relative risk (RR), 3.9) or >50 years (RR, 2.7), the higher mefloquine dose (M25) (RR, 2.7), vomiting <24 hours before enrolment (RR, 2.5), axillary temperature >38.0 °C (RR, 1.6), and parasitaemia $>10\ 000/\mu\text{l}$ (RR, 1.3). In children ≤ 2 years, 30% vomited with M25, and 13% did not tolerate a repeat dose. Vomiting was reduced 40% by splitting the higher dose (RR, 0.6; 95% CI, 0.4–0.8), and 50% by giving mefloquine on the second day in combination with artesunate (RR, 0.5; CI, 0.3–0.9). Anorexia, nausea, vomiting, dizziness, and sleeping disorders were 1.1–1.4 times more frequent with M25 than M15 in the three days following treatment, but were similar in the single or split-dose M25 groups, despite twofold higher mefloquine concentrations obtained with the latter. There was no evidence that diarrhoea, headache, and abdominal pain were associated with mefloquine use. High-dose mefloquine is well tolerated but should be given as a split dose.

Introduction

Mefloquine, a quinoline-methanol antimalarial which is effective against multidrug-resistant strains of *Plasmodium falciparum*, is being used increasingly for the treatment and prevention of falciparum malaria in many parts of the world, particularly south-east Asia (1). As with the structurally related cinchona alkaloids (quinine, quinidine), minor side-effects following mefloquine treatment are more common than with the other available antimalarials such as chloroquine (2, 3), halofantrine (4), sulfadoxine-pyrimethamine (FansidarTM) (5, 6), and the

qinghaosu derivatives (7). Nevertheless, mefloquine treatment is usually well tolerated and most adverse events are mild and restricted to gastrointestinal side-effects, fatigue, feelings of dissociation, and dizziness (8). However, diarrhoea and vomiting, shortly after mefloquine administration, have been reported to occur in as many as 50% and 30% of patients, respectively. Both are associated with reduced oral bioavailability and an increased risk of subsequent treatment failure (4, 9–19). These adverse events, although mild, are therefore important when considering the formulation of treatment regimens for a potentially life-threatening disease. They are particularly important where there is reduced sensitivity to mefloquine, such as in Thailand, where resistance has necessitated an increase in the recommended treatment dose from 15 to 25 mg/kg (19, 20). It is uncertain if the higher dose augments the risk of early vomiting or diarrhoea, or if the incidence of side-effects can be reduced by splitting the dose in two or more administrations, as is currently recommended by the manufacturer. Single-dose regimens have obvious practical advantages in the tropics where compliance with multiple-dose regimens is poor, in particular with antimalarial drugs which have a relatively high frequency of side-effects.

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Over the past five years we have treated over 3500 patients with symptomatic falciparum malaria with various mefloquine regimens in a series of prospective treatment studies conducted in multidrug-resistant areas along the Thai–Myanmar and Thai–Cambodian borders. An evaluation of the dose-related risk for serious neuropsychiatric adverse events following mefloquine treatment has been published elsewhere (21). The present study describes in detail the frequency and duration of mild to moderate side-effects observed in these patients, defines the risk groups, and evaluates the relative merits of split- and single-dose regimens.

Patients and methods

Study site

This study was part of a series of prospective anti-malarial treatment trials conducted between 1990 and 1994, some of which have been reported previously (4, 7, 16, 18–20, 22). They took place in camps for displaced persons on the Thai–Myanmar border (Shoklo and Maela) and Thai–Cambodian border (Site-B) where *P. falciparum* is resistant to all the widely available antimalarial drugs. Health care in these camps is provided by the aid organization Médecins sans Frontières (MSF). Since 1986, mefloquine has been the drug of choice for the treatment of microscopically confirmed uncomplicated falciparum malaria in these camps. At first, mefloquine was available only in combination with sulfadoxine–pyrimethamine (MSP), but since 1991 it has been used alone.

Study procedures

Patients presenting to the outpatient clinics of Médecins sans Frontières (MSF) were enrolled into the respective studies if they had falciparum malaria, weighed over 8 kg (Myanmar border: until 1992) or 5 kg (Cambodian border), and had no signs of severe malaria (23). Pregnant women were not included. Informed consent was obtained from the patients, or their parents or guardians. These studies were approved by the Ethical Committee of the Faculty of Tropical Medicine, Mahidol University, and the Karen Refugee Committee, Mae Sod, Thailand.

The methods used for assessing mefloquine efficacy and toxicity were the same in all treatment studies, except that in the first study ($n=395$) daily follow-up was not done in the first week. Before treatment was started, a detailed history was taken specifically to assess the presence of general malaise, fatigue, muscle/joint pains, headache, anorexia, nausea, vomiting, abdominal pain, diarrhoea, dizziness,

and sleeping disorders. On admission a basic clinical examination was performed and the liver, spleen size and axillary temperature were recorded. Patients were then treated with either 15 or 25 mg/kg of mefloquine in various regimens (Table 1). Between 1990 and 1991 mefloquine (25 mg/kg) as monotherapy (M25), or combined with artesunate (4–10 mg/kg), was also given as retreatment to patients with infections that had recrudesced after primary treatment with any of the mefloquine 15 mg/kg regimens.

Mefloquine (Lariam®, 250 mg base tablets, Hoffman La-Roche, Basle, Switzerland) was given according to the calculated dose per kg body weight. For adults and older children, this was to the nearest quarter tablet. Some of the younger children received mefloquine orally by syringe as a suspension of crushed tablets in sugar water. All febrile patients with an axillary temperature $\geq 37.5^\circ\text{C}$ received paracetamol 15 mg/kg before mefloquine administration, and those with high-grade fevers were also given tepid sponging. In a subgroup of 1000 patients the changes in axillary temperature before paracetamol, and just before drug administration (1/2–2 hours later) were recorded to assess the efficacy of paracetamol in reducing fever. Each drug administration was supervised and the full dose of mefloquine was repeated if vomiting occurred within one hour following administration of 15 or 10 mg/kg, or within half an hour following a single dose of 25 mg/kg. To reduce the risk of 'overtreatment', only half the mefloquine dose was repeated if vomiting occurred between 30 and 60 minutes following a single dose of 25 mg/kg.

Patients were seen daily until aparasitaemic and then again on days 7, 14, 21 and 28. At each follow-up visit a history of clinical illness was taken, a side-effects questionnaire was completed, and the axillary temperature, and spleen and liver size were recorded. Blood was taken by fingerprick for determination of the parasite count. In a subgroup of patients a blood sample was taken on days 0, 3, 7, 14, 21, and 28 for haematology ($n=171$), biochemistry ($n=128$), and mefloquine blood levels ($n=183$). Mefloquine concentrations were measured by high-performance liquid chromatography (HPLC) (24). All patients who failed to improve clinically and who remained parasitaemic, and all patients with a positive blood smear on or after days 7–9 were considered as treatment failures.

Statistical analysis

Data were analysed using the statistical programmes Epi Info (CDC Public Domain Software) and SPSS (SPSS Benelux Inc., Gorinchem, Netherlands). Proportions were compared by the χ^2 test or Fisher's

exact test. The adjusted relative risks presented were calculated using Mantel-Haenszel weighted cross-tabulations. Normally distributed continuous data were compared by the Student's *t*-test and one-way analysis of variance.

Logistic regression. Stepwise logistic regression was used to assess the relationship between mefloquine dose and possible side-effects while controlling for markers of disease severity. A post-treatment model was constructed for each symptom in which the presence or absence of the symptom between day 1 and 3 was entered as the dependent variable, and the effect of each mefloquine regimen (M15 and M25, split or single dose) evaluated while controlling for the presence or absence of the symptom on admission (i.e., pre-treatment). Body temperature and parasite densities were significantly associated with symptomatology independent of age and they were included in the model as markers of 'disease status'. Where indicated, this was done using an interaction term of admission body temperature and parasite count, where patients with axillary temperatures $>38.0^{\circ}\text{C}$ or parasitaemias $>10\,000/\mu\text{l}$ were classified as having 'moderate' disease, and those with lower values as 'mild'. The prevalence of some of the symptoms was significantly associated with age and sex, and differed also by study location. Since these variables were not equally distributed over the different treatment groups they were included as independent variables in the model to correct for potential confounding. Age correction was done using the following three age strata: young children aged <5 years, older children aged 5–14 years, and adults >14 years. To allow for the change in disease status over time after treatment, the highest temperature recorded between days 1–3 was also entered in the model as a dichotomous variable with 37.5°C used as cut-off. Mefloquine dose, age, and the presence or absence of the symptom on admission were always forced into the model. The post-treatment temperature, camp, sex and the interaction term for disease severity were all entered in the initial model but only included in the final model if they significantly improved its predictive value independently from the other variables.

Resolution of symptoms and side-effects. This was assessed by survival analysis. The time needed for 50% (T_{50}) of the symptomatic patients to become asymptomatic was used as a marker for the duration of the side-effects and was calculated using survival analysis. 'Life tables' of the daily proportion of patients in whom the side-effect or symptoms had cleared were constructed and the cumulative incidence calculated by the product-limit method (25).

The T_{50} values presented were estimated by fitting a sigmoid E_{max} model to the cumulative data, and were compared by the Mantel-Haenszel log rank test, weighted for age.

Results

Data from 3673 patients were available for analysis of side-effects following mefloquine treatment. These included 3493 patients who received mefloquine on day 0 and 180 patients who received a single dose of M25 at 24 hours combined with artesunate (MA-3) (Table 1); 445 out of the 3493 patients received mefloquine as retreatment.

Early vomiting (within 1 hour)

The incidence of early vomiting in the 475 patients who received M15 or M25 simultaneously with the first dose of artesunate (M15_a and M25_a) was similar to that found in patients who received mefloquine alone (M15_m and M25_m) (RR, 1.02; 95% confidence intervals (CI), 0.70–1.50, stratified by age and dose).

Table 1: Characteristics of mefloquine treatment regimens involved in the study of risk factors associated with early vomiting

Regimen	Name	No. of patients
<i>Mefloquine 15 mg/kg, single dose:</i>		
1. M15 single dose combined with sulfadoxine-pyrimethamine	MSP	568
2. M15 single dose, monotherapy	M15 _m	170
3. M15 single dose stat. combined with 10 mg/kg artesunate (3.3 mg/kg, 8 hourly)	M15 _a	324
Total	M15	1062
<i>Mefloquine 25 mg/kg, single dose:</i>		
4. M25 single dose, monotherapy	M25 _m	1730
5. M25 single dose combined with artesunate 4 mg/kg stat.	M25 _a	151
Total	M25 ₁	1881
<i>Mefloquine 25 mg/kg, split dose:</i>		
6. M25 monotherapy, as split dose; 15 mg/kg stat. followed by 10 mg/kg at 16–24 h	M25 ₂	550
Total	M25 ₂	550
Total day 0 treatments	—	3493
7. M25 single dose at 24 hours combined with artesunate 10 mg/kg over 3 days	MA-3	180
Grand total		3673

Vomiting after the combination MSP, which contains 15 mg/kg of mefloquine, was also equally likely as after M15_m (age-adjusted RR, 0.91; CI, 0.56–1.50). Previous treatment with mefloquine in the last month ($n=445$) did not increase the risk of vomiting (age- and dose-adjusted RR, 1.16; CI, 0.82–1.65). Retreatments and these combination regimens were therefore included in the further analysis of early vomiting, and pooled with the patients who received mefloquine alone.

Overall, on admission 236 out of the 3493 (6.8%) treated patients vomited within the first hour following treatment. A quarter of them vomited immediately, 71% within the first 10 minutes, and 86%, 92%, 98% and 100% within 30, 40, 50 and 60 minutes respectively. All patients who had vomited received a repeat dose, but 70 of the 236 (30%) vomited again, and this increased to 51% if a second repeat dose was given to these patients.

Early vomiting was dose-related and occurred 2.67 (1.87–3.83) times more frequently after treatment with a single dose of 25 mg/kg than with 15 mg/kg (Fig. 1, Table 2). The risk of early vomiting could be almost halved by splitting the dose (RR, 0.57; CI, 0.38–0.84; $P = 0.006$, $n=1538$, adjusted for age, disease severity, and history of vomiting). Only 1% of the patients in the split-dose group vomited both the first dose (15 mg/kg) and the second dose (10 mg/kg).

Risk groups for early vomiting. Young children under 7 years ($n=713$), and elderly patients aged over 50 years ($n=67$) were more likely to vomit than those aged 7–50 years ($n=2713$) (≤ 6 years: RR, 3.88; 95% CI, 2.87–5.24) (>50 years: RR, 2.67; CI, 1.17–6.09). The highest incidence occurred in the very young children aged ≤ 2 years ($n=207$) (M25₁: 32/106 (30%), M25₂: 9/45 (20%) and M15: 11/56 (20%)) (Fig. 1). Overall, 7% of the M25₁, 6% of the M25₂ and 5.4% of the M15-treated children ≤ 6 years vomited the repeat dose (14%, 10%, and 5% in ≤ 2 year-olds). The corresponding figures in the patients aged 7–50 years were 0.6%, 0.5% and 1%, and in the >50 -years age group they were 4%, 11% and 5%. Early vomiting was equally likely to occur in those children aged ≤ 6 years who had received mefloquine as a suspension or as tablets (RR, 1.04; CI, 0.61–1.77).

Vomiting was related to disease severity independently from age, and was associated with higher parasitaemias and a history of vomiting in the previous 24 hours. The risk was twofold higher in patients with body temperature exceeding 38.0 °C at the time of enrolment (Table 2). Paracetamol 1/2–2 hours before mefloquine administration successfully reduced body temperature below 37.5 °C in 86% and below 38.0 °C in 96% of these patients. Patients

whose fever came down were as likely to vomit the mefloquine dose as the afebrile patients. In patients who received mefloquine–artesunate combinations, mefloquine-associated early vomiting was reduced twofold (RR, 0.49; 95% CI, 0.26–0.90) when it was given on day 1, i.e., 24 hours after administration of artesunate. Parasitaemia had declined by $>90\%$ in the majority of these patients, and most were afebrile by the time mefloquine was administered.

Late side-effects (onset >1 hour)

Dose relationship. Questionnaires on symptoms and side-effects were evaluated from 1462 patients with mefloquine monotherapy, of whom 166 received M15, 871 M25₁, and 425 M25₂. All patients treated with the combination mefloquine–artesunate or MSP were excluded from this analysis. The clinical and

Fig. 1. The relationship between age and the incidence (%) of vomiting, within one hour and from days 1 to 3 following treatment with a single dose of either 15 mg/kg mefloquine (M15), or 25 mg/kg (M25₁), or 25 mg/kg given as 15 mg/kg stat. followed by 10 mg/kg the next day (M25₂).

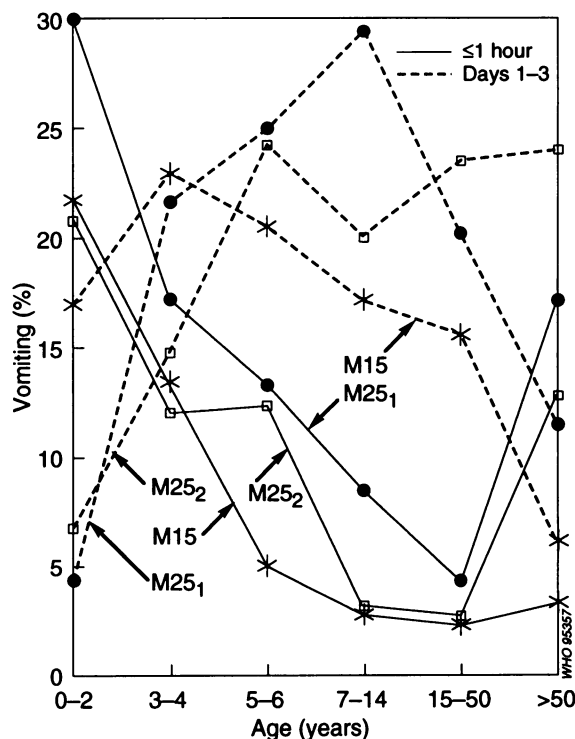


Table 2: Risk factors associated with early vomiting (≤ 1 hour) following treatment with a single dose of mefloquine alone (LariamTM)

	Vomiting	Crude RR ^a	Adjusted RR ^a
Age:			
(a) ≤ 6 or >50 years	121/780 (15.5) ^b	3.82 (2.99–4.89) ^b	3.50 (2.57–4.75) ^b
(b) 6–50 years	101/2712 (3.7)	<i>P</i> <0.00001 ^c	<i>P</i> <0.00001 ^c
Vomiting last 24 hours:			
(a) Yes	71/433 (16.4)	3.47 (2.61–4.61)	2.47 (1.83–3.35)
(b) No	101/2135 (4.7)	<i>P</i> <0.00001	<i>P</i> <0.00001
Mefloquine dose:			
(a) 25 mg/kg	160/1891 (8.5)	1.93 (1.47–2.53)	2.67 (1.87–3.83)
(b) 15 mg/kg	71/1612 (4.4)	<i>P</i> <0.00001	<i>P</i> <0.00001
Temperature:			
(a) >38.0 °C	97/878 (11.0)	2.05 (1.58–2.67)	1.55 (1.14–2.10)
(b) ≤ 38.0 °C	111/2064 (5.4)	<i>P</i> <0.00001	<i>P</i> = 0.006
Parasite count:			
(a) $\geq 10\ 000/\text{mm}^3$	93/939 (9.9)	1.93 (1.49–2.51)	1.33 (0.98–1.79)
(b) $<10\ 000/\text{mm}^3$	123/2403 (5.1)	<i>P</i> <0.00001	<i>P</i> = 0.08

^a Relative risk associated with the presence of the risk factor (a) when compared to its absence (b) [crude RR] after adjustment for the other factors given in the table [adjusted RR].

^b Figures in parentheses are percentages; those in italics are the 95% confidence intervals of the relative risk.

^c *P* values were calculated from Mantel-Haenszel summary chi-squared statistic.

laboratory characteristics for the three treatment groups on admission are given in Table 3. All symptoms/side-effects were correlated significantly with admission parasitaemia and body temperature on enrolment and with the rate of fever clearance after treatment. Not surprisingly, the strongest predictor of the occurrence of the symptom or side-effect after treatment was its presence on admission. Multivariate analysis adjusting for the presence or absence of the symptom on admission, disease severity, age, location, and post-treatment temperature showed that anorexia, nausea, late vomiting (>1 h), and dizziness (adults only) were significantly more frequent and lasted longer in the higher-dose group (Fig. 2 and Table 4). The relative strengths of the association between mefloquine dose and the occurrence of the side-effects were compared by their odds ratios, which showed that nausea and vomiting were most strongly associated with the dosage of mefloquine, followed by dizziness (adults) and anorexia. General malaise, headache, abdominal pain, muscle/joint pain, and diarrhoea were equally likely following M25 or M15 (Table 4). Fatigue was significantly less frequent in the high-dose group, but if present, it lasted significantly longer than in the M15 group. There was no significant correlation between the mefloquine concentration on day 3 and the number of reported side-effects in the first 3 days ($n=183$).

Split versus single dose. In contrast to the significant reduction in the risk of early vomiting, no reduction in later side-effects was seen by splitting the mefloquine dose. As expected, patients in the M25₂ group reported fewer side-effects following the first dose of 15 mg/kg, but by day 3 an equal number of patients in the M25₁ and M25₂ group had reported dizziness or gastrointestinal side-effects (Fig. 2).

Severe dizziness and sleeping disorders. Data on sleep disorders was available from 336 patients (aged >4 years) enrolled in studies commencing after 1992, in which specific questioning on sleep patterns were included. On admission, 1% of patients complained of difficulty in sleeping but this increased to 4.3% after treatment with M25₁ ($P = 0.01$). None complained of sleeping problems on day 7. Details on the severity of dizziness were available from 580 patients (332 adults) treated with M25₁. On admission, 34% of the children and 63% of the adults complained of mild dizziness, 1.6% and 2.6% of moderate dizziness (feeling of swaying or rotation), and none of severe dizziness (i.e., associated with difficulty in walking unaided). Between day 1 and 3, these figures were 39%, 6% and 3% for children, and 60%, 15%, and 5% for adults, i.e., a significant increase in the prevalence of moderate and severe dizziness ($P < 0.0001$). In most cases (84%) the

Table 3: Clinical and laboratory variables of patients on admission: analysis of late side-effects (>1 hour after treatment with mefloquine monotherapy)

	Dosage regimen: ^a			
	M15	M25 _p	M25 _i	M25 ₂
No. of patients	166	1298	873	425
No. of males	111 (66.9) ^b	801 (61.7)	557 (63.8)	244 (57.4) ^c
Age in years: median/range	17.5/0.6–53	15/0.4–88	16/0.4–88	13/0.5–60 ^c
No. by age group:				
≤4 years	18 (10.8) ^b	142 (10.9)	88 (10.1)	54 (12.7) ^c
4–14 years	49 (29.5)	484 (37.3)	298 (34.1)	186 (43.8)
>14 years	99 (59.6)	672 (51.8)	487 (55.8)	185 (43.5)
Camp Site-B	70 (42.2)	110 (8.5) ^d	110 (12.6)	0 (—) ^c
Maala	33 (19.9)	358 (27.6)	251 (28.8)	106 (24.9)
Shoklo	63 (38.0)	831 (64.0)	512 (58.6)	319 (75.1)
No. with <1 month mefloquine intake	10 (6.0)	212 (16.3) ^d	121 (13.9)	91 (21.4) ^c
Parasitaemia/mm ³ : Geometric mean	4948 (3981–6151)	3650 ^d (3296–4040)	3450 (3042–3914)	4042 (3401–4803)
No. with ≥10 000/mm ³	54 (32.5)	405 (31.2)	261 (29.9)	144 (33.9)
Temperature °C: mean ± SD	38.0 ± 1.0	37.8 ± 1.0 ^d	37.7 ± 1.1	37.8 ± 0.9
No. with >38.0 °C	85 (51.2)	527 (40.6) ^d	347 (39.7)	180 (42.4)

^a M15 = mefloquine 15 mg/kg, single dose; M25_p = M25_i + M25₂ pooled; M25_i = mefloquine 25 mg/kg, single dose; M25₂ = mefloquine 25 mg/kg, given as 15 mg/kg stat. followed by 10 mg/kg the next day.

^b Figures in parentheses are percentages; those in italics are 95% confidence intervals.

^c Significantly different from M25_i ($P < 0.05$).

^d Significantly different from M15 ($P < 0.05$).

severe episodes began within 24 hours, and 76% had resolved within 1 day. All had resolved within 3 days.

Age, sex and pretreatment. There were important differences in the frequency of reported symptoms/side-effects between children and adults. Vomiting (0–14-year-olds) and diarrhoea (0–4-year-olds) were significantly more common in children than in adults on admission (adjusted odds ratio (OR), 0.75 and 0.32, respectively; $P < 0.05$ for both). However, for vomiting this ratio inverted after the start of treatment; adults vomited significantly more between days 1 and 3 than young children (0–4 years) (OR, 2.1) and with equal frequency as older children (OR, 1.1) ($P < 0.05$). Thus, whereas mefloquine-associated vomiting within 1 hour was a particular problem in the youngest age group, later vomiting was most prominent among older children and adults. The frequency of late vomiting was consistently lower in the youngest children ≤2 years, compared with older patients for all three dose regimens (Fig. 1). Anorexia, and dizziness were reported most frequently in adults both on admission (OR, 1.3 and 3.7) and

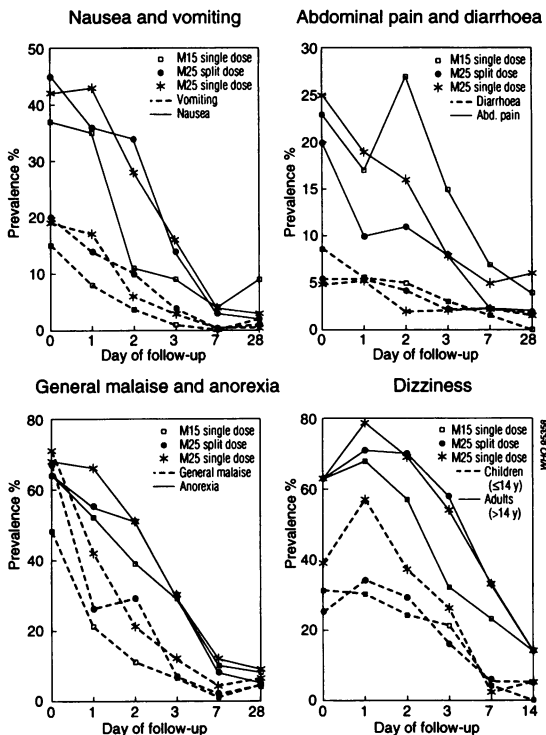
also after treatment (OR, 1.4 and 3.8, respectively ($P < 0.05$ for both)).

Adult females complained significantly more than adult males of anorexia (OR, 1.18), nausea (OR, 1.31), vomiting (OR, 1.41) and dizziness (OR, 1.25) on admission. The odds ratios remained about the same after the start of treatment except for vomiting and were 1.24, 1.38, 1.04, and 1.21, respectively, post-treatment. Previous treatment with mefloquine within the last month did not increase the risk of mild adverse events.

Diarrhoea

Overall, post-treatment diarrhoea occurred in 6.6% of patients treated with mefloquine monotherapy and in 4.6% between days 1 and 7, (i.e., after peak mefloquine concentrations had been reached). There was no evidence that the occurrence of diarrhoea was dose-related. The prevalence of post-treatment diarrhoea was even slightly higher in the M15 group, but this difference was not significant (Table 4). The majority of the patients with post-treatment diarrhoea did not have diarrhoea on admission. The proportion

Fig. 2. The age-adjusted prevalence of symptoms and side-effects following a single dose of mefloquine 15 mg/kg (M15) or 25 mg/kg (M25₁), or 25 mg/kg given as 15 mg/kg stat. followed by 10 mg/kg the next day (M25₂).



of patients in whom the onset of diarrhoea was after the start of treatment was similar in both dose groups (M15, 79%; M25, 76%), as was the time by which diarrhoea had resolved in 50% of the cases (Table 4).

Skin reactions

There were no serious cutaneous reactions following 545 MSP treatments and 2955 treatments with mefloquine alone. Four out of 1067 (0.4%) patients, for whom details were available, developed urticarial rashes which were classified as mild and disappeared spontaneously in all cases within days.

Biochemistry and haematology

Sequential analysis of the haematological ($n=171$) and biochemical parameters ($n=128$) have been reported previously (18, 20). There were no significant differences in the proportions of patients with abnormal values among those treated with M15_a

(containing 15 mg/kg of mefloquine combined with artesunate), M25₂ or M25₁, and there were no abnormalities other than those expected in uncomplicated falciparum malaria.

ECG findings

Electrocardiograms were taken on enrolment and on days 3, 7, 14, 21 and 28 in patients treated with M25₁ or MA-3. There was no difference on admission or post-treatment in any of the ECG parameters between the treatment groups, and data have therefore been pooled for further analysis. Bradycardia (<60 heart beats/min) occurred in 4/110 (3.6%) of the adults on admission. This proportion increased significantly to 17% (4/23) by day 3 ($P=0.03$) and 26% (11/43) by day 7 ($P<0.001$); 18% (3/17) still had bradycardia on day 14, and only 7% (1/15) on days 21 or 28. None of 98 children had bradycardia on admission or day 3, and only 3% (1/31) had bradycardia on day 7 and none afterwards. The background prevalence of bradycardia in this population was 8/85 (9.4% in untreated healthy adult controls, i.e., 2.7 (1.2–6.3) times less than on day 7 in the patients ($P=0.03$).

Discussion

Mefloquine is probably the most studied of all the antimalarial drugs. A considerable amount of information on the tolerance of mefloquine has been reported previously in the medical literature and this was reviewed recently (8, 26). The aim of the current study was to provide a confident assessment of the risks and benefits of the high-dose mefloquine regimen (25 mg/kg) currently required for radical cure of falciparum malaria on the eastern and western borders of Thailand (19, 20). An evaluation of the dose-related risk for severe neuropsychiatric adverse events following mefloquine treatment has been published elsewhere (21).

Early vomiting (within one hour) and diarrhoea were previously found to be important factors determining treatment outcome in this area and together explained (at current levels of resistance) 24% of the early treatment failure (\leq day 9) in children treated with a single dose of mefloquine 25 mg/kg (10). The current study allowed the identification of patients at risk for diarrhoea or early vomiting. Overall, 8.5% of the patients vomited the higher dose of mefloquine when it was given as a single administration, which is significantly higher than with other antimalarials such as halofantrine (4), artesunate (7), or chloroquine (3). Early vomiting was strongly related to disease severity, a history of vomiting in the previous 24

Table 4: Symptoms and side-effects (>1 hour after treatment) following treatment with three different mefloquine monotherapy regimens^a, with T₅₀ values^b and odds ratios^c

Symptom	Day	Children (≤14 years) ^d			Adults			All age groups		
		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
Anorexia:		2.8	2.9	2.3	3.0	3.2	1.5 ^e	2.9	3.1	1.9 ^e
T ₅₀ (days)										
M25 ₁ /M25 ₂	0	1.05 (0.87–1.27)			1.30 (1.07–1.58)			1.14 (1.00–1.31)		
	1–3	1.19 (0.98–1.43)			1.22 (0.97–1.53)			1.20 (1.03–1.38)		
M25 _p /M15	0	1.12 (0.84–1.49)			0.98 (0.76–1.28)			1.03 (0.85–1.24)		
	1–3	1.27 (0.95–1.69)			1.30 (1.00–1.70)			1.24 (1.02–1.50)		
Nausea:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		1.7	2.0	1.1	1.9	2.3	1.2 ^e	1.8	2.1	1.2 ^e
M25 ₁ /M25 ₂	0	1.12 (0.91–1.39)			0.94 (0.78–1.13)			1.02 (0.88–1.17)		
	1–3	1.03 (0.83–1.28)			1.12 (0.92–1.35)			1.08 (0.94–1.24)		
M25 _p /M15	0	1.43 (0.97–2.09)			1.08 (0.83–1.40)			1.19 (0.96–1.47)		
	1–3	1.83 (1.15–2.91)			1.27 (0.97–1.66)			1.36 (1.08–1.71)		
Vomiting:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		1.2	1.1	0.8 ^e	1.3	1.7	1.0 ^e	1.2	1.4	0.8 ^e
M25 ₁ /M25 ₂	0	1.04 (0.86–1.26)			1.15 (0.89–1.48)			1.07 (0.92–1.25)		
	1–3	1.20 (0.97–1.49)			0.92 (0.75–1.15)			1.06 (0.91–1.24)		
M25 _p /M15	0	1.40 (1.01–1.94)			1.05 (0.78–1.42)			1.20 (0.96–1.50)		
	1–3	1.90 (1.18–3.06)			1.08 (0.78–1.48)			1.32 (1.02–1.70)		
Diarrhoea:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		2.7	1.8	1.9	1.5	1.6	1.2	2.0	1.6	1.4
M25 ₁ /M25 ₂	0	0.91 (0.62–1.33)			1.12 (0.72–1.74)			0.97 (0.72–1.30)		
	1–3	1.27 (0.91–1.77)			1.36 (0.97–1.92)			1.25 (0.98–1.58)		
M25 _p /M15	0	0.93 (0.56–1.54)			0.73 (0.49–1.08)			0.81 (0.60–1.10)		
	1–3	0.99 (0.62–1.59)			1.11 (0.77–1.62)			1.10 (0.82–1.47)		
Dizziness:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		2.5	2.5	2.2	7.4	5.7	3.2 ^e	5.4	4.5	2.7 ^e
M25 ₁ /M25 ₂	0	1.24 (0.99–1.55)			1.00 (1.83–1.21)			1.09 (0.95–1.26)		
	1–3	0.99 (0.78–1.24)			1.13 (0.90–1.44)			1.05 (0.89–1.24)		
M25 _p /M15	0	0.89 (0.64–1.25)			0.72 (0.56–0.93)			0.79 (0.65–0.96)		
	1–3	0.90 (0.64–1.29)			1.37 (1.03–1.82)			1.12 (0.89–1.41)		
General malaise:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		1.2	0.9	0.9	1.4	1.0	1.2	1.3	1.0	1.1
M25 ₁ /M25 ₂	0	1.25 (1.03–1.51)			1.23 (0.99–1.52)			1.22 (1.06–1.41)		
	1–3	1.37 (1.11–1.70)			1.45 (1.18–1.78)			1.25 (0.98–1.58)		
M25 _p /M15	0	1.70 (1.25–2.31)			1.95 (1.36–2.80)			1.80 (1.43–2.28)		
	1–3	1.28 (0.85–1.93)			1.19 (0.81–1.75)			1.18 (0.90–1.56)		
Abdominal pain:		M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15	M25 ₁	M25 ₂	M15
T ₅₀ (days)		1.6	2.1	1.9	2.0	1.3	3.3 ^e	1.8	1.5	2.2 ^e
M25 ₁ /M25 ₂	0	1.29 (1.00–1.67)			1.22 (0.97–1.54)			1.26 (1.06–1.49)		
	1–3	1.13 (0.86–1.48)			1.47 (1.11–1.93)			1.30 (1.07–1.57)		
M25 _p /M15	0	0.67 (0.23–1.94)			0.99 (0.74–1.32)			0.94 (0.71–1.25)		
	1–3	0.73 (0.34–1.57)			0.60 (0.44–0.81)			0.60 (0.45–0.79)		

^a M25₁ = mefloquine 25 mg/kg single dose; M25₂ = mefloquine 25 mg/kg, given as 15 Mg/kg stat. followed by 10 mg/kg the next day; M15 = mefloquine 15 mg/kg, single dose; M25_p = M25₁ + M25₂ pooled.

^b The T₅₀ values represent the time needed for 50% of the symptomatic patients to become asymptomatic, i.e., the median clearance time. The T₅₀ values were estimated by survival analysis.

^c Odds ratios (OR) for the occurrence of symptoms and side-effects on admission (day 0) and post-treatment (days 1–3) for three treatment regimens containing mefloquine. The odds ratios (95% confidence intervals) shown are adjusted for age, sex, study location, history of mefloquine intake, and disease severity. They were calculated using logistic regression. M25₁/M25₂ = odds ratio for M25₁ versus M25₂; M25_p/M15 = odds ratio for M25_p versus M15.

^d Young children unable to answer the questions of nausea, dizziness, and abdominal pain were excluded (≤4 years).

^e Significant difference ($P < 0.05$) between T₅₀ values of M25_p and M15. None of the differences between the T₅₀ values of M25₁ and M25₂ was significant.

hours, and age. It was a particular problem in young children (≤ 6 years), but also in the elderly (> 50 years). Early vomiting was most frequent (30%) in the very young (aged ≤ 2 years). This is similar to the 35% vomiting rate reported in Malawian children of this age group (12). It was also dose-dependent and 2.7 times more frequent after a single dose of 25 mg/kg than after 15 mg/kg (95% CI, 1.9–3.9). The risk of vomiting was not increased when artesunate (a qinghaosu derivative) was given simultaneously, despite the large number of additional tablets which had to be swallowed if both drugs were administered at the same time.

We evaluated several approaches to reduce the incidence of vomiting. The risk increased when body temperature rose above 38.0 °C, but there was no relationship between vomiting and temperatures below this value. Paracetamol and tepid sponging successfully reduced temperatures to below 38.0 °C in 96% of cases, and eliminated higher grade fevers (> 38.5 °C). Although there was no control group for comparison, this suggests that paracetamol is very effective in acute falciparum malaria and that measures to reduce body temperature below 38 °C would potentially be beneficial in reducing the risk of vomiting. If mefloquine was given combined with artesunate it was best to administer the mefloquine dose on the second day (at 24 hours) rather than on admission. This reduced the rate of vomiting twofold (RR, 0.5; 95% CI, 0.3–0.9), because many patients had recovered clinically by 24 hours, following the rapid antimalarial effect of the qinghaosu derivative. A similar reduction was seen if the 25 mg/kg mefloquine dose was split into a first dose of 15 mg/kg, followed by 10 mg/kg the next day.

We have shown previously that by splitting the high-dose regimen mefloquine concentrations by day 3 are double those obtained after a single dose (27). The current studies show that these higher concentrations do not lead to a higher incidence of side-effects. This suggests that besides dose, the rate at which peak concentrations are reached is an important determinant of mefloquine tolerance. The benefits associated with the higher drug levels obtained with the split dose outweigh the practical advantage gained by a single dose in this multidrug-resistant area where increasingly higher mefloquine concentrations are needed to obtain radical cure. Emphasis should thus be placed on instruction of health personnel and patients explaining the risks associated with low compliance.

Among the later (beyond one hour) symptoms and possible side-effects, nausea and vomiting, followed by dizziness and anorexia and sleeping disorders were found to be associated with mefloquine. Dizziness was the most prominent and occurred in

80% of patients treated with the higher dose; 15% complained of vertigo and 5% of the adults were unable to walk unaided, a major problem in this mountainous area. This lasted usually one day and had resolved in all patients by the fourth day.

Both malaria and mefloquine contribute to the occurrence of symptoms post-treatment, and it is difficult to determine their relative contributions. However, a causal relationship with mefloquine is suggested by the significant dose effect after correction for markers of disease status and the fact that these symptoms occurred more frequently following mefloquine than other antimalarial drugs such as halofantrine, which gives similar time for the fever to abate (4). In this previous study, fatigue was also associated with mefloquine, but in the current study there was no evidence that this was dose-related. Although the reported fatigue took significantly longer to resolve in the high-dose group, its overall incidence between day 1 and 3 was less than with the lower dose of mefloquine. General malaise, headache, muscle/joint pain, and abdominal pain were all strongly associated with disease severity, but there was no evidence that they were related to mefloquine use.

Diarrhoea was equally likely following 15 mg/kg or 25 mg/kg doses, and following a split or single dose, and much less common (7%) in this large series of patients compared with the 50% previously reported in Thai patients and volunteers (11). The difference in formulation between the current commercial compound (Lariam®) and the old formulation used in these initial studies,^a which was produced by the Walter Reed Army Institute of Research, may explain this discrepancy. Diarrhoea was related to acute malaria and may thus be unavoidable in a number of mefloquine-treated patients. There have been a number of studies which indicated that diarrhoea is an important risk factor of treatment failure following mefloquine (10, 11, 15). Patients with diarrhoea after treatment should therefore be monitored carefully and treated again with alternative antimalarials when the parasites fail to clear (10).

Bradycardia (< 60 heart beats/min) and sinus arrhythmia are commonly reported to the manufacturer and WHO as a side-effect attributed to mefloquine and have been a consistent finding occurring in up to 68% of the patients in hospital-based studies in Thailand (9, 28, 29) and Zambia (2).

Bradycardia is usually observed 3 to 7 days after the start of treatment when fever has re-

^a Centers for Disease Control. *Adverse events associated with mefloquine*. Meeting on mefloquine toxicity, Atlanta, GA, USA, 13–14 May 1991 (unpublished).

solved. However, profound bradycardia (35–40 heart beats per min) and sinus arrhythmia occur as part of the normal physiological response in healthy subjects at rest and may be particularly frequent in hospital-based studies when previously fit, young adults are confined to bed. In the current study, bradycardia occurred in 26% of the adults on day 7, which was more than on admission (4%) or at convalescence (7%), and more than the background incidence of bradycardia in healthy adults in this population (9%, $P = 0.03$). It is not possible to distinguish in this study whether post-treatment bradycardia was induced by mefloquine or related to the recovery from acute falciparum malaria. However, comparative treatment studies in Thailand and Zambia reported similar rates of bradycardia in mefloquine-treated patients compared with rates in those treated with chloroquine (2), halofantrine (22), or artesunate (30). Furthermore, a recent study comparing the cardiotoxicity of mefloquine between patients and healthy volunteers concluded that the causal relationship with mefloquine is uncertain and postulated that both bradycardia and sinus arrhythmia may be a normal physiological phenomenon in patients recovering from acute malaria (31). Mefloquine may or may not induce bradycardia, but this remains asymptomatic and is not a clinical problem; furthermore, there is no evidence of heart rhythm disturbances associated with mefloquine treatment.

International guidelines as yet make no provision for the use of mefloquine in children weighing less than 15 kg (32). This is because little information exists on its safety, tolerance, and dosage regimen for treatment in this age group. Children weighing between 5 and 15 kg were not excluded from the current study because of compliance problems with the 7-day quinine regimen, and its unacceptably high failure rate in Thailand, even when given supervised (4, 20). The assessment of toxicity in children aged ≤ 2 years is notoriously difficult, and this study was not designed specifically for this purpose. However, we could compare the incidence of diarrhoea, loss of appetite, and vomiting with that in older patients. Diarrhoea was more common in this age group both on admission and post-treatment, but this was not associated with the mefloquine dose. The incidence of anorexia was similar to that in older children and late vomiting was relatively rare, even in the high-dose group and was half as common as in adults. The principal adverse effect in the age group ≤ 2 years was early vomiting; 30% vomited shortly after mefloquine intake and 46% vomited a second time. Overall, 13% did not tolerate 25 mg/kg mefloquine and 5% did not tolerate 15 mg/kg. These rates were high despite good nursing care by well-trained local staff, and may even be higher in busy outpatient set-

tings. More detailed studies specifically designed to assess the tolerance and pharmacokinetics of mefloquine in this age group are ongoing, but this initial analysis and that in the Malawian children (12) suggests that alternative formulations or methods for administration of mefloquine may benefit this age group.

As with prophylaxis (33), women reported more side-effects than men, but they also reported more symptoms on enrolment. Previous treatment with mefloquine did not increase the incidence of the commonly reported side-effects. Many of these patients with recrudescence infection had low parasite counts and were less symptomatic compared with patients who received primary treatment. However, patients with recrudescence infections following initial mefloquine treatment were at a more than 7-fold increased risk of a severe neuropsychiatric reaction when treated again with mefloquine 25 mg/kg (21).

Overall, high-dose mefloquine was well tolerated by adults and children > 2 years, but should be given after reduction of fever and as a split dose to reduce the risk of early vomiting and enhance drug absorption.

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Résumé

Traitement du paludisme à falciparum aigu par la méfloquine: étude prospective des effets indésirables bénins chez 3673 patients

Entre 1990 et 1994, une série d'études prospectives ont été réalisées afin d'optimiser le traite-

ment du paludisme à falciparum polypharmacorésistant dans les zones frontalières de la Thaïlande avec le Myanmar et le Cambodge. Au total, 3673 patients ont été traités par divers schémas thérapeutiques contenant de la méfloquine à raison de 15 mg/kg (M15) ou 25 mg/kg (M25). Le but de la présente étude était d'évaluer la tolérance à la méfloquine à forte dose (25 mg/kg) actuellement nécessaire pour le traitement radical du paludisme à *P. falciparum* dans ces régions. Comme il a été observé que la diarrhée après traitement et les vomissements précoces suivant l'administration de méfloquine (<1 heure, malgré la réadministration du traitement) sont des déterminants importants de l'issue du traitement, nous avons évalué plusieurs approches destinées à réduire les vomissements précoces et avons défini les groupes à risque pour la diarrhée.

Globalement, 7% des malades ont eu des vomissements dans l'heure suivant l'administration de méfloquine. Les facteurs de risque pour les vomissements précoces étaient l'âge ≤ 6 ans (RR=3,9) ou >50 ans (RR=2,7), la méfloquine à dose élevée (M25 : RR=2,7), la présence de vomissements dans les 24 heures précédant l'inclusion dans l'étude (RR=2,5), une température axillaire $>38,0^\circ\text{C}$ (RR=1,6), et une parasitémie $>10\,000/\mu\text{l}$ (RR=1,3). Chez les enfants de ≤ 2 ans, 3% ont vomi la dose de M25 et 13% n'ont pas supporté l'administration d'une deuxième dose. La prise de méfloquine sous forme de suspension ne diminuait pas l'incidence des vomissements, alors qu'on obtenait une réduction de 40% en divisant la dose la plus forte en deux doses fractionnées données à 16–24 heures d'intervalle (RR=0,6; IC 95%=0,4–0,8). On a également pu obtenir une réduction de 50% des vomissements précoces en donnant la méfloquine le deuxième jour en association avec de l'artésunate (RR=0,5; IC 95%=0,3–0,9) dans tous les groupes d'âge. Un bassinage à l'eau tiède associé à la prise de paracétamol 1/2 heure à deux heures avant l'administration de méfloquine permettait d'abaisser la température au-dessous de $38,0^\circ\text{C}$ chez 96% des sujets fébriles.

Les effets secondaires observés dans les trois jours suivant le traitement consistaient en troubles digestifs, vertiges et troubles du sommeil. Ils étaient 1,1–1,4 fois plus fréquents avec la dose M25 qu'avec la dose M15, et étaient analogues dans les groupes M25 recevant la dose entière ou fractionnée. Ces observations conduisent à penser qu'en dehors de la dose, la vitesse à laquelle la concentration maximale est atteinte est un déterminant important de la tolérance à la méfloquine. Les nausées et vomissements étaient les

effets secondaires les plus marqués chez les enfants, et les vertiges chez les adultes; 66% des adultes traités par M25 présentaient des vertiges légers à modérés lors de l'admission dans l'étude et 75% après le traitement; 5% d'entre eux étaient incapables de marcher sans aide après le traitement, ce qui n'était observé chez aucun d'eux à l'admission dans l'étude. Les vertiges graves duraient habituellement une journée au maximum. La survenue d'une diarrhée après traitement (7%) était aussi fréquente avec les doses de 15 que de 25 mg/kg. La diarrhée est toutefois associée au paludisme à falciparum aigu et peut donc être inévitable chez un certain nombre de patients. La bradycardie, qui était présente chez 5% des adultes à l'admission et chez 26% le jour 7 ($p<0,001$) était asymptomatique et ne posait pas de problèmes cliniques. On ne sait pas si la méfloquine elle-même ou la guérison du paludisme était à l'origine de cette observation. Aucune autre anomalie de l'ECG n'a été notée.

La méfloquine à forte dose est bien tolérée chez les malades de plus de 2 ans, mais doit être administrée après avoir fait baisser la fièvre et sous forme de doses fractionnées afin de réduire le risque de vomissements et d'améliorer l'absorption du médicament.

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